## REMARKS

The requisite fee of $1110.00 for a three-month extension of time and any other fees that may be due in connection with the filing of this paper or with this application should be charged to Deposit Account No. 02-1818. If a Petition for Extension of Time is needed, this paper is to be considered such Petition. A Petition pursuant to 37 C.F.R. § 1.132 is provided.

Claims 1-35, 37-52, 54-84, 86-136 and 138 are pending. Claim 36 is cancelled without prejudice or disclaimer. Claims 121-125 and 132-136, directed to non-elected subject matter, are withdrawn from further consideration. Claims 5, 11, 19-24, 29, 35, 37-45, 47-52, 54-84, 86-98, 100-106, 109-119, 127 and 129 are withdrawn from further consideration as allegedly directed to a nonelected species, there being no allowable generic or linking claim at this time.

Claims 1 and 121 are amended to more distinctly claim the subject matter. Claims 1 and 121 are amended to replace the recitation "derivative" with the recitation "salt, ester, enol ether, enol ester, solvate or hydrate." Basis for the amendment is found throughout the specification (*e.g.*, see page 9, lines 19-21 and page 23, line 21 through page 24, line 20). No new matter is added.

### I. REJOINDER OF CLAIMS THAT READ ON THE ELECTED SPECIES

The Action states that claims 35 and 128 do not read on the elected species. Applicant respectfully disagrees. Claim 35 recites that $R_6$ if fluoro. Because the aromatic ring is freely rotatable about its axis of connection, when rotated 180°, the fluoro group would occupy the position of substituent $R_2$. Hence, claim 35 reads on the elected species. Applicant respectfully requests that claim 35 be rejoined with claims 1-4, 6-10, 12-18, 25-28, 30-34, 36, 46, 99, 107, 108, 120, 130, 131 and 138.

Claim 128 recites that the compound of claim 1 is a selective glucocorticoid receptor agonist. In the response to the Restriction requirement, Applicant identified claim 128 as reading on the elected species. The Examiner has provided no reasoning why claim 128 is believed to not read on the elected species. Applicant respectfully requests that the rationale for withdrawing claim 128 be provided so that Applicant can address it with particularity, or in the alternative, that claim 35 be rejoined with claims 1-4, 6-10, 12-18, 25-28, 30-34, 36, 46, 99, 107, 108, 120, 130, 131 and 138.

### II. INFORMALITIES

#### 1. Declaration

The Action alleges that the Declaration is defective because it allegedly does not identify the mailing address of each inventor. Applicant respectfully submits that the

Examiner is mistaken. The Declaration as filed provides the mailing address for each inventor. The Examiner is directed to the second line of the Declaration, which recites:

**Our residences, post office addresses and citizenships are as stated below next to our names.**

Accordingly, the address presented next to each inventor's name is the inventor's post office address. The post office address is the address at which the inventor customarily receives his or her mail. Hence, the declaration provides the mailing address for each inventor. Therefore, the Declaration is not defective.

**2. Title of the Application**

The Examiner alleges that the title of the application is not descriptive because it does not clearly indicate the subject matter the claims. The Examiner suggests amending the title to recite: 1,2-Dihydro-9-hydroxy-10-methoxy-1,2,4- trimethyl-5*H*-chromeno[3,4-*f*]quinoline Compounds that Modulate Glucocorticoid Receptors.

Applicant wishes to thank the Examiner for the suggested title. As amended herein, the title has been amended to recite: 5-substituted-1,2-Dihydro-9-hydroxy-10-methoxy-1,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline Compounds that Modulate Glucocorticoid Receptors. Thus, the amendment of the application obviates the objection.

**3. Claim 36**

Claim 36 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claim 36 is cancelled herein. Hence, the objection is moot.

**II. THE REJECTION OF CLAIMS UNDER 35 U.S.C. §112, SECOND PARAGRAPH**

Claims 1-4, 6-10, 12-18, 25-28, 30-34, 36, 46, 120, 126, 128, 130, 131 and 138 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleges that it in not clear whether the exclusion phrases at the end of the claim apply to "derivatives" of a compound of Formula I.

Reconsideration and withdrawal of this rejection is respectfully requested in view of the amendments herein and the following remarks.

**Relevant Law**

Claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. *Rosemount Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), *Caterpillar Tractor Co. v. Berco, S.P.A.*, 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). A claim is not indefinite

when one skilled in the art would understand the language in the claims when read in light of the specification. 35 U.S.C. § 112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. Claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. *Shatterproof Glass Corp. v. Libby-Owens Ford Col.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), cert. dismissed, 106 S.Ct. 340 (1985).

**Analysis**

Claim 1 and its dependent claims are rejected as being indefinite because the Examiner alleges that it is unclear whether the exclusion phrases at the end of the claim apply to "derivatives" of a compound of Formula I and whether certain "derivatives" are excluded. Applicant respectfully submits that the specification states that a "pharmaceutically acceptable derivative" of a compound includes salts, esters, enol ethers, enol esters, acetals, ketals, orthoesters, hemiacetals, hemiketals, acids, bases, solvates, hydrates or prodrugs thereof (*e.g.*, see page 23, lines 19-21). Thus, it respectfully is submitted that, when read in light of the specification, the skilled artisan would understand the meaning of the recitation "pharmaceutically acceptable derivative" as recited in claim 1 to refer to a salt, ester, enol ether, enol ester, acetal, ketal, orthoester, hemiacetal, hemiketal, acid, base, solvate, hydrate or prodrug of a compound of formula I of claim 1, which includes the provisos within the body of the claim.

The compound of Coghlan *et al.* (WO02/02565) referred to by the Examiner is not a salt, ester, enol ether, enol ester, acetal, ketal, orthoester, hemiacetal, hemiketal, acid, base, solvate, hydrate or prodrug of a compound of formula I of claim 1. Thus, the compound of Coghlan *et al.* is not a "derivative" as defined in the instant specification. The Examiner admits that the exclusion phrases at the end of claim 1 exclude the compound of Coghlan *et al.* from within the scope of the claims. Thus, when read in light of the specification, the skilled artisan would not consider the compound of Coghlan *et al.* to be within the scope of the instant claims.

Applicant respectfully submits that one of skill in the art would understand the language and scope of the claims when read in light of the specification and readily would be able to determine the metes and bounds of claim 1 and its dependent claims. Accordingly, the claims are not indefinite when read in light of the specification.

Notwithstanding the above, in order to advance the application to allowance, claim 1 is amended to replace the recitation "derivative" with derivatives recited in the specification.

## III. THE REJECTION OF CLAIMS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-4, 6-10, 12-18, 25-28, 30-34, 36, 46, 120, 126, 128, 130, 131 and 138 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner alleges the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner acknowledges that the application provides written description of formula I compounds. The Examiner alleges that the description does not extend beyond formula I compounds to demonstrate that Applicant was in possession of the "genus of derivatives" of formula I compounds as claimed.

None of the pending claims include the recitation "derivatives" and thus none of the pending claims recite a "genus of derivatives" as alleged by the Examiner. Hence, none of the pending claims is within the purview of this rejection. Therefore, amendment of claim 1 renders this ground of rejection moot.

## IV. THE REJECTION OF CLAIMS UNDER 35 U.S.C. §102(b)

Claims 1-4, 6-10, 12-18, 25-28, 30-34, 36, 46, 120, 126, 128, 130, 131 and 138 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Coghlan *et al* . (WO02/02565) based on construing claim 1 in the broadest reasonable terms, where the exclusion of the last two lines on claim 1 applies to a compound of formula I, but not to a "derivative" of a compound of formula I. The Examiner states that the compound described in Example 373 of Coghlan *et al.* is excluded from within the scope of formula I, but could be construed to be a "derivative" of compound I and thus is considered to be within the metes and bounds of the instant claims.

Reconsideration of the grounds for the rejection is respectfully requested in view of the amendments herein and the following remarks.

### RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is

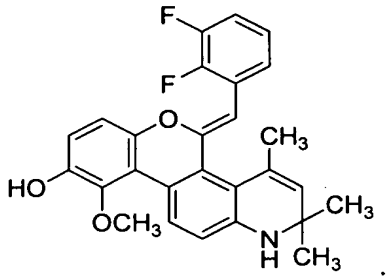
incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

**THE CLAIMS**

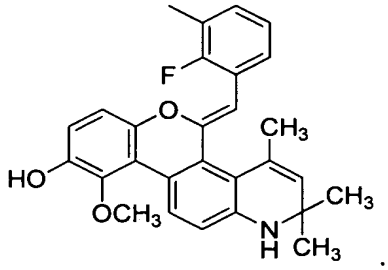
The claims are discussed in a related section above. None of the pending claims include the recitation "derivative thereof."

**Disclosure of Coghlan *et al.* and differences from the claimed subject matter**

Coghlan *et al.* discloses glucocorticoid receptor-selective benzopyrano[3,4-*f*]-quinolines. Coghlan *et al.* describes a 2,3-difluorophenyl derivative in Example 373, which has the structure:




The compound elected for search purposes in the instant application has the following structure:




Claim 1 of the instant claims recites that if any two positions selected from among $R_2$, $R_3$, $R_4$, $R_5$, and $R_6$ are both F, then at least one of the other three positions selected from $R_2$, $R_3$, $R_4$, $R_5$, and $R_6$ is not hydrogen. Therefore, the cited compound of Coghlan *et al.* is excluded from the instant claims. Coghlan *et al.* does not disclose any compound within the scope of the claims.

**ANALYSIS**

The Examiner admits that the compound described in Example 373 of Coghlan *et al.* is excluded from the scope of the instant claims. None of the pending claims recites a

"derivative" of a compound of formula I. Hence, the grounds for the rejection, that the compound described in Coghlan *et al.* could be construed to be a "derivative" of compound I and thus be within the metes and bounds of the instant claims, is inapt. The compound described in Example 373 of Coghlan *et al.* is excluded from the scope of the instant claims. Coghlan *et al.* does not describe any compound that is within the scope of the instant claims.

Accordingly, for at least these reasons, Coghlan *et al.* does not disclose every element of independent claim 1. Claims 2-4, 6-10, 12-18, 25-28, 30-34, 36, 46, 120, 126, 128, 130, 131 and 138 ultimately depend from claim 1 and include every limitation thereof. Thus, Coghlan *et al.* does not disclose every element of claims 1-4, 6-10, 12-18, 25-28, 30-34, 36, 46, 120, 126, 128, 130, 131 and 138. Therefore, Coghlan *et al.* does not anticipate any of claims 1-4, 6-10, 12-18, 25-28, 30-34, 36, 46, 120, 126, 128, 130, 131 and 138.

## V. THE REJECTION OF CLAIMS UNDER 35 U.S.C. §103(a)

Claims 1-4, 6-10, 12-18, 25-28, 30-34, 36, 46, 99, 107-108, 120, 126, 128, 130, 131 and 138 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Coghlan *et al.* (WO 02/02565 A2; 2002) in view of Patani *et al.* ("Bioisosterism: A Rational Approach in Drug Design"; 1996; Chem. Rev.; 96:3147-3176) because Coghlan allegedly teaches a compound with the same core structure of Formula I, where $R_1$ is Formula II and $R_2$ and $R_3$ are both F, and $R_4$-$R_6$ are each H, which allegedly is a 2,3-difluoro analog of the elected compound, and Patani teaches bioisosteres that elicit similar biological activity, due to common physico-chemical properties of the bioisosteres. The Examiner alleges that it would have been obvious to one of ordinary skill to modify the 2,3-difluoro compound of Coghlan (Example 373) by substituting a methyl group for the F at the 3-phenyl position, which would have resulted in the elected compound, in light of the teachings of Patani. This rejection respectfully is traversed.

**Relevant Law**

For *prima facie* obviousness of claimed subject matter to be established under 35 U.S.C. §103, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). This principle of U.S. law regarding obviousness was **not** altered by the recent Supreme Court holding in KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727, 82 USPQ2d 1385 (2007). In KSR, the Supreme Court stated that "Section 103 forbids issuance of a patent when 'the differences between the subject matter sought to be patented and the prior art are such the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.'" KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1734, 82 USPQ2d 1385, 1391 (2007).

The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); see, also, In re Papesch, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963). Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). In addition, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

Furthermore, the Supreme Court in KSR took the opportunity to reiterate a second long-standing principle of U.S. law: that a holding of obviousness requires the fact finder (here, the Examiner), to make explicit the analysis supporting a rejection under 35 U.S.C. 103, stating that "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. Id. at 1740-41, 82 USPQ2d at 1396 (citing In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)).

While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. KSR, 127 S. Ct. at 1731. The court stated in dicta that, where there is a

> "market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try **might** show that it was obvious under § 103."

In a post-KSR decision, PharmaStem Therapeutics. Inc. v. ViaCell. Inc., 491 F.3d 1342 (Fed. Cir. 2007), the Federal Circuit stated that:

> an invention would not be invalid for obviousness if the inventor would have been motivated to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. Likewise, an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Furthermore, KSR has not overruled existing case law. See In re Papesch, (315 F.2d 381, 137 USPQ 43 (CCPA 1963)) and In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991). "In cases involving new compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." Takeda v. Alphapharm, 492 F.3d 1350 (Fed. Cir. 2007).

The disclosure of the applicant cannot be used to hunt through the prior art for the claimed elements and then combine them as claimed. In re Laskowski, 871 F.2d 115, 117, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

**The Claims**

The claims are discussed in a related section above.

**The teachings of the cited art and differences from the claimed subject matter.**

**Coghlan *et al.***

The teachings of Coghlan *et al.* are discussed above.

**Patani *et al.***

Patani *et al.* teaches bioisosterism in drug design. Patani *et al.* teaches that under Grimm's hydride replacement law, fluorine, hydroxyl, amino and methyl groups are interchangeable and would be expected to have similar biological properties. Patani *et al.* does not teach what effects are observed if a F atom is replaced with a methyl group, which has an effective van der Waal's radii larger than a F atom (see Tables 9 and 11). Patani *et al.* does not teach or suggest replacing a F atom on a phenyl ring with a methyl group. Patani *et al.* only teaches that fluorine, hydroxyl, amino and methyl groups are expected to be interchangeable under Grimm's hydride replacement law.

**ANALYSIS**

**The combination of the teachings of Coghlan *et al.* with Patani *et al.* does not result in the claimed compounds.**

Coghlan *et al.* describes the compound 5-(2,3-difluoromethylbenzylidene)-1,2-dihydro-9-hydroxy-10-methoxy-1,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline, which includes a pendent phenyl ring substituted at positions 2 and 3 with a F atom. The species elected for search purposes in the instant application differs from the cited compound of

Coghlan *et al.* in that it has a pendent phenyl ring that includes a F atom at position 2 and a methyl substituent at position 3. The Examiner alleges that replacing a F atom with a methyl group is a minor structural modification, and that because a methyl group is a classical isostere for a F atom, that one of ordinary skill in the art would have expected a compound so-modified to have the same pharmacological activity as the compound in Coghlan *et al.*

In addition to the 2,3-difluorophenyl substituent, the cited compound of Coghlan *et al.* has five other substituents on the core structure: one hydroxyl group, a methoxy group and three methyl groups. There is no teaching or suggestion in Patani *et al.* to select a F atom of the pendent phenyl group and replace it with a methyl group. Patani *et al.* merely teaches that a F atom, a hydroxyl, an amino and a methyl group theoretically are interchangeable under Grimm's hydride replacement law. Thus, under Grimm's hydride replacement law, at least six different substituents on the cited compound of Coghlan *et al.* (the hydroxyl group or any one of the three methyl groups of the core structure or any one of the two F atoms on the pendent phenyl ring) could be modified by replacing one or all of the substituents with one of a F atom, a hydroxyl, an amino or a methyl group. This leads to a large number (four selections at six positions = $4^6$ or 4,096) of possible compounds that could be obtained by isosteric substitution of six of the substituents on the cited compound in Coghlan *et al.* with the theoretical isosteric moieties (a F atom, a hydroxyl, an amino and a methyl group) described in Patani *et al.*. There is no teaching or suggestion in Coghlan *et al.* or Patani *et al.* to select the compound of Example 373 of Coghlan *et al.* as a starting structure, and to modify that compound by replacing only the F atom at position 3 on the pendent phenyl ring with a methyl group while retaining the F atom at position 2 of the phenyl ring and leaving the hydroxy group and all of the methyl groups of the core structure unchanged.

The structurally closest analogs of the instantly claimed compounds described in Coghlan *et al.* are substituted at position 2, 2 and 3 or position 4 with a F atom. The instant compounds of formula I can include substituents not taught or suggested in Coghlan *et al.* or Patani *et al.* For example, the instant compounds having a pendent phenyl group can be substituted at position 2 of the phenyl ring with a substituent selected from among CN, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted haloalkyl, an optionally substituted heteroalkyl, $-CONR_{14}R_{15}$, $-OR_{16}$, $-COR_{16}$, $-SR_{16}$, $-SO_2NR_{14}R_{15}$, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl and an optionally substituted cycloalkyl. The instant compounds having a pendent phenyl group can be substituted at position 3 of the phenyl ring with a

substituent selected from among CN, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted haloalkyl, an optionally substituted heteroalkyl, -$OR_{16}$, -$SR_{16}$, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl and an optionally substituted cycloalkyl. The instant compounds having a pendent phenyl group can be substituted at position 4 of the phenyl ring with a substituent selected from CN, -$OR_{16}$, -$SR_{16}$, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted haloalkyl, an optionally substituted heteroalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl and an optionally substituted cycloalkyl. Neither Coghlan *et al.* nor Patani *et al.* teaches or suggests replacing a F atom on a pendent pheny ring of a 1,2-Dihydro-9-hydroxy-10-methoxy-1,2,4- trimethyl-5*H*-chromeno[3,4-*f*]quinoline with such substituents.

In addition, the instantly claimed genus of compounds includes compounds of formula I substituted at $R_1$ with an optionally substituted pyridinyl moiety or with an optionally substituted heterocyclic 5-membered ring. Neither Coghlan *et al.* nor Patani *et al.* teaches or suggests replacing the pendent phenyl ring of the compounds of Examples 372-374 of Coghlan *et al.* with an optionally substituted pyridinyl moiety or with an optionally substituted heterocyclic 5-membered ring or that such compounds would retain glucocorticoid modulating activity. Therefore, the combination of teachings of Coghlan *et al.* nor Patani *et al.* does result in the instantly claimed compounds. The Examiner has failed to set forth a *prima facie* case of obviousness.

**Notwithstanding the above, the attached Declaration of Dr. Zhi demonstrates results not taught or suggested by the combination of teachings of the cited references.**

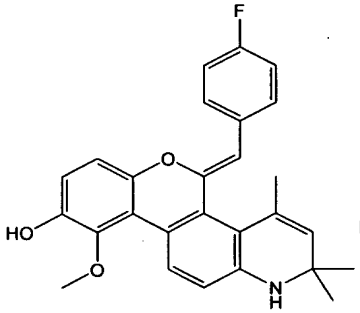
Notwithstanding the fact that the combination of teachings of the references fails to teach or suggest modifying the compound of Coghlan *et al.* in order to arrive at a compound within the instant claims, Applicant respectfully submits that, as shown in the attached Declaration from Dr. Zhi, an inventor of the claimed subject matter, when the properties of the compounds of the instant claims are compared to the structurally closest analogs of Coghlan *et al.*, the compounds within the scope of the instant claims demonstrate properties that are different from the closest prior art compounds and that are not taught or suggested in Coghlan *et al.* or Patani *et al.* The combination of teachings of the reference does not teach or suggest the results achieved thereby. These results include decrease in PR binding and significant improvement in the GR/PR selectivity of the instant compounds compared to their closest structural analogs.

**DECLARATION**

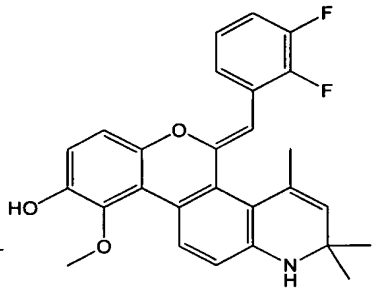
The DECLARATION of Dr. Lin Zhi provides data that shows that the closest compounds of Coghlan *et al.* to the compounds of formula I of claim 1, exhibit properties not taught or suggested by Coghlan *et al.* In particular, compounds within the scope of claim 1 were compared to the compounds of Coghlan *et al.* that are the closest structural analogs of formula I. The compounds compared were those of the instant application that are closest in structure to the Coghlan *et al.* compounds. The DECLARATION demonstrates that compounds of formula I of claim 1 in which the substituents on the moiety of $R_1$ is modified demonstrate enhanced glucocorticoid modulating properties compared to the compounds of Coghlan *et al.*

In particular, the DECLARATION shows that modification of the substituent on the moiety at the position corresponding to $R_1$ of formula I of claim 1, such as replacing a F atom on a phenyl ring with a methyl group, results in compounds that exhibit (1) decreased PR binding when compared to structural analogs having a F atom at the corresponding position and (2) a significant improvement in the GR/PR selectivity.

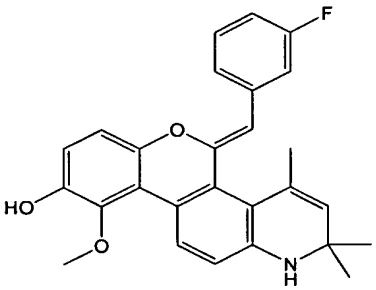
As stated in the DECLARATION, the closest structural analogs in Coghlan *et al.* are the compounds described in Examples 372-374 of Coghlan *et al.*, which have the following structures:



Example 372 of Coghlan *et al.*



Example 373 of Coghlan *et al.*



Example 374 of Coghlan *et al.*

The compound described in Example 372 of Coghlan *et al.* is structurally similar to the compound described in Example 9 of the instant application, but the compound within the scope of the instant claims has a methyl group at position 4 of the pendent phenyl ring instead of a F atom. The compound described in Example 373 of Coghlan *et al.* is structurally similar to the compound described in Example 18 of the instant application, but the compound within the scope of the instant claims has a methyl group at position 3 of the pendent phenyl ring instead of a F atom. The compound described in Example 374 of Coghlan *et al.* is structurally similar to the compound described in Example 8 of the instant

application, but the compound within the scope of the instant claims has a methyl group at position 3 of the pendent phenyl ring instead of a F atom.

As discussed in the DECLARATION and below, the compounds of the instant application demonstrate significantly improved receptor selectivity between the glucocorticoid receptor and the progesterone receptor compared to their closest structural analogs described in the examples of Coghlan *et al.*

Compounds within the scope of the claims were tested and compared to their closest structural analogs described in Coghlan *et al.* The compounds were tested for GR binding, PR binding and GR/PR selectivity. As shown in the results provided in the DECLARATION, the compounds of the instant claims exhibit properties not demonstrated by the closest prior art compounds described in Coghlan *et al.* Replacing a F atom of the phenyl ring of the closest structural analogs described in Coghlan *et al.* with a methyl group does not result in compounds having equivalent properties as the Office Action suggests would be expected from bioisosteric replacement of a F atom with a methyl group. Instead, as shown in the DECLARATION, the instant compounds with a methyl group at position 4 of the phenyl ring instead of a F atom (Example 9) or a methyl group at position 3 of the phenyl ring instead of a F atom (Example 18) demonstrate decreased PR binding and significantly improved GR/PR selectivity when compared to their closest structural analogs described in Coghlan *et al.* (compounds of Examples 372 and 373). The compounds of Coghlan *et al.* that are the closest structural analogs of the compounds of formula I of claim 1 have a GR/PR selectivity of 90-91. Compounds within the scope of the instant claims that are structural analogs of the compounds of Examples 372 and 373 or Coghlan *et al.* with a methyl group on the pendent phenyl ring instead of a F atom have a GR/PR selectivity of from 372-734. Thus, compounds within the scope of the instant claims with a methyl group on the pendent phenyl ring instead of a F atom demonstrate about a 3-fold to 8.5-fold decrease in PR binding and a 2-fold to 8-fold improvement in the GR/PR selectivity compared to the compounds described in Coghlan *et al.* The data for the compound of Example 8 of the instant application, which has a methyl group on the pendent phenyl ring, shows the same general trend: a decreased PR binding and improved GR/PR selectivity compared to the tested compounds of Coghlan *et al.*

Hence, the compounds of formula I of claim 1 of the instant application exhibit properties not possessed by the closest prior art structural analogs described in Coghlan *et al.* Replacing the F atom at position 4 of the phenyl ring of the compound of Example 372 of Coghlan *et al.* with a methyl group (Example 9 of the above-captioned application), or

replacing the F atom at position 2 of the phenyl ring of the compound of Example 373 of Coghlan *et al.* with a methyl group (Example 18 of the above-captioned application) results in compounds having properties very different from compounds of Coghlan *et al.* that have a F atom at the corresponding position. Since compounds of formula I of claim 1 structurally closest to compounds of Coghlan *et al* were compared, and each of the compounds of formula I of claim 1 exhibited decreased PR binding and greater GR/PR selectivity than the Coghlan *at al.* structural analogs, the compounds of formula I of claim 1 possess properties not taught or suggested in Coghlan *et al.* Patani *et al.* does not teach or suggest that compounds of formula I of claim 1 should have decreased PR binding or greater GR/PR selectivity compared to the compounds of Coghlan *et al.* because Patani *et al.* teaches that an F atom and a methyl group are interchangeable substituents. Therefore, the DECLARATION demonstrates that the compounds of formula I of claim 1 possess properties not taught or suggested by the cited art.

Thus, for any and all of these reasons, the combination of Coghlan *et al.* and Patani *et al.* does not teach or suggest every element of independent claim 1. Claims 2-4, 6-10, 12-18, 25-28, 30-34, 36, 46, 120, 126, 128, 130, 131 and 138 ultimately depend from claim 1 and include every limitation thereof. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness of any of the pending claims, including claims 1-4, 6-10, 12-18, 25-28, 30-34, 36, 46, 120, 126, 128, 130, 131 and 138. Applicant respectfully requests reconsideration of this rejection.

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In view of the amendments and remarks herein, reconsideration and allowance respectfully are requested.

Respectfully submitted,

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